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EXAMINER	
PORTNER, VIRGINIA ALLEN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,233	MEYER ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *24,25,27,28 and 30-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *24-25, 27-28, 30-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ ~~Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)~~ Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ ~~Notice of Informal Patent Application (PTO-152)~~
6) ☐ Other: _____.

DETAILED ACTION

Claims 24-25, 27-28, 30-39 are pending.

Rejections Withdrawn

1. Claims 24-39 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production and induction of an immune response in an immunocompetent mammal utilizing a recombinant attenuated Salmonella cell that expresses Helicobacter urease A or B or A and B immunogens, does not reasonably provide enablement for the production of recombinant attenuated Salmonella that comprise a heterologous coding sequence for a fragment of Helicobacter urease that is only immunoreactive and is not an immunogen for induction of a antibody or a protective immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, has been obviated through amendment of the claims to recite the term "immunogen" rather than immunoreactive fragment..

2. Claims 24,26-29, 31 and 33 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in light of the cancellation of claims 26 and 29, and amendment of claims 14, 27, 28, 31 and 33 to recite the claimed invention clearly.

Rejections Maintained

3. Claims 24-25, 30-39 rejected under 35 U.S.C. 102(b) as being anticipated by Fulginiti et al (1995), for reasons of record in paper number 31, dated August 01, 2003.

4. Claims 24, 33-35 rejected under 35 U.S.C. 102(e) as being anticipated by Michetti et al (US Pat. 6,290,962), for reasons of record in paper number 31, dated August 01, 2003.

5. Claims 30-32 and 36-39 rejected under 35 U.S.C. 102(e) as being anticipated by Michetti et al (US Pat. 6,290,962), for reasons of record in paper number 31, dated August 01, 2003.

6. Claims 24, 33-35 rejected under 35 U.S.C. 102(b) as being anticipated by Michetti et al (WO95/22987), for reasons of record in paper number 31, dated August 01, 2003.

7. Claims 24-25, 27-28,33-35 rejected under 35 U.S.C. 103(a) as being unpatentable over Michetti et al (WO95') in view of Russell et al (US Pat. 6,030,624) for reasons of record in paper number 31, dated August 01, 2003.

Response to Arguments

8. The rejection of claims 24-25, 29-39 under 35 U.S.C. 102(b) as being anticipated by Fulginiti et al (1995), is traversed on the grounds that:

a. "that there is no disclosure of a protective vaccine in Fulginiti"

b. "it cannot be determined from Fulginiti's disclosure whether "urease" means urease A, B or both";

c. "no details of the expression system pPX5024 are indicated"; and

d. concludes the abstract is "not enabled by the cited disclosure".

9. It is the position of the examiner that the attenuated AroA Salmonella vaccine strain SL3261 (see Fulginiti, line 5), was considered to be a vaccine strain for Salmonella, and to be a strain for the expression of foreign genes when presented to an animal as an oral vaccine (see Fulginiti, lines 1-2). Therefore the composition when administered to an animal was considered to be a vaccine composition. Gomez-Duarte et al (1998) is being cited as evidence that

Salmonella strain SL3261 (see title, abstract), the very strain used by Fulginiti et al, induced a protective immune response upon expressing H.pylori urease when administered as a single oral dose composition.

10. With respect to the recitation of urease in the Fulginiti et al reference, it is the position of the examiner that the attenuated Salmonella expressed "H.pylori urease". H.pylori urease is a molecule that evidences urease activity, and would contain all of the components essential for urease activity, which would include both subunits Ure-A and Ure-B; the subunits when combined together evidence "urease" activity. The control for the administered recombinantly expressed urease was the native form of H.pylori urease (see Fulginiti, line 10 and line 24), which would be an appropriate control for the recombinantly expressed corresponding Helicobacter pylori urease.

While the examiner believes the attenuated Salmonella expressed recombinant H.pylori urease (title of reference) , the instantly claimed invention encompasses the administration of immunogenic fragments of urease A and urease B. The number and type of fragments are not specifically recited and therefore read on the administration of a immunogenic fragments of either urease A and urease B. Clearly the recombinantly expressed H.pylori urease was immunogenic as the recombinant urease induced "an IgG2a response" which is a Th-1 type immune response, an immune response that has been shown to be associated with induction of protection against infection (see Guy et al, 1998, page 855, paragraph 3: "strong Th1 responses conferred a high level of protection against H.pylori infection in mice") .

The Salmonella strain SL3261 has been known in the art since the early 90's (see US Pat. 5,961,983, column 10, Table 2 and is a Salmonella typhimurium strain with an Aro A mutation).

The amino acid (P14916 and P14917, Ure-A and Ure-B, respectively) and nucleic acid sequences for H.pylori urease were made public in 1990; the sequences were publically known and available prior to the filing date of the instant Application.

Therefore the arbitrary designation of "pPX5024" for the plasmid that carried the nucleic acid coding sequences of H.pylori urease is not critical, because plasmid constructs which will express heterologous nucleic acid sequences in a host cell were known in the art (see Fulginiti, line 1), the nucleic acid sequence(s) for H.pylori urease was known (evidence provided by Swiss-Prot print outs), the AroA Salmonella strain SL3261 was known (Brey et al (US Pat. 5,961,983)), the dosage concentration was described (10^{10}, line 7), the urease coding sequences in the plasmid were expressed due to an expression signal in the plasmid ("expressing foreign genes", line 1), and urease was expressed to a sufficient level that an IgG2a immune response directed against H.pylori urease was stimulated (see Fulginiti, line 29). Gomez-Duarte et al provides evidence that Salmonella strain SL3261 expressing H.pylori urease induces a protective immune response (reference provided herewith). The Fulginiti et al reference is enabling and still inherently anticipates the instantly claimed invention. See In re Atlas, case law cited in last action.

11. The rejection of claims 24, 33-35 (composition) and claims 30-32 and 36-39 (Method) under 35 U.S.C. 102(e) as being anticipated by Michetti et al (US Pat. 6,290,962), is traversed on the grounds that:

e. "Michetti discloses the use of both subunits separately in the production of vectors" and

f. "does not suggest that they be used together"; and concludes

g. based upon data presented in Michetti, (see Tables 2-7) "a person skilled in the art would not consider the combination of UreA and UreB in view of Michetti's disclosure."

12. It is the position of the examiner that:

Michetti et al disclose and teach the recombinant expression of Helicobacter urease (both A& B subunits) together by an live vaccine Salmonella vector

(see col. 17, lines 12-67 especially, "whole urease" col. 17, line 19" and col. 18, lines 1-67, especially lines 9-19 "The discussion herein focuses on the use of urease naturally produced by Helicobacter pylori (section B) . However, it will be appreciated that the urease or subunits or constructs thereof mentioned above, capable of eliciting the desired protective immune response, may be produced by recombinant DNA techniques well known in the art").

Michetti et al discloses that urease subunits A &B act together to induce a protective immune response:

"We have identified the urease antigen of Helicobacter pylori as a candidate vaccine and demonstrated its efficacy in an animal model. We have also demonstrated the use of the Helicobacter pylori urease antigen for treatment and eradication of Helicobacter infection" (see col. 7, lines 15-25).

The Michetti et al reference goes on to teach a combination of urease peptides, which are immunogenic fragments of subunits A and B in the production of recombinant attenuated expression vectors:

(see col. 7, lines 19-21 (urease or B-subunit) ;see col. 7, lines 46-52 ("a mixture of peptides and/or proteins)"; see col. 10, lines 14-17 ("host immunized with a urease, preferably Helicobacter pylori urease or Helicobacter pylori urease B subunit"); see col. 11, lines 33-52 ("The mucosal adjuvant may also be genetically or chemically linked to the urease peptides.")

It is also the position of the examiner that Michetti et al teach the utilization of both urease subunits ("whole urease", see col. 19, line 51-62) for the induction of a protective immune

response (col. 7, lines 16-25) produced recombinantly (see col. 17, line 17) in a live Salmonella typhimurium or typhi vaccine vector (see col. 18: line 11, lines 28-30, lines 38-39).

Finally, based on the complete disclosure, guidance, teaching and prior experiments referenced and described by Michetti et al, and not just the data presented in Tables 2-7, the person of skill in the art would consider the combination of UreA and UreB because Michetti et al had already demonstrated whole urease to be a protective Helicobacter pylori antigen (see col. 7, lines 16-20), and teaches the recombinant production of whole urease, which comprises both urease A & B subunits, as well as a mixture of urease A & B fragment immunogenic protective peptides (see col. 17, lines 45-53, "as a whole protein") expressed in a live vaccine vector, specifically Salmonella (see col. 18, lines 38-39).

13. Applicant at page 9, paragraph 2, of the Amendment in response to the Office Action dated August 1, 2003, asserts that "Since there is no specific disclosure of Salmonella cells expressing Helicobacter antigens in Michetti, a skilled person might assume that the recombinant urease is delivered by surface exposure and secretion." And concludes, "A skilled person might doubt whether this can be achieved with recombinant Salmonella".

14. It is the position of the examiner that Michetti et al discloses an enabled embodiment of f a recombinant Salmonella live vaccine vector that would comprise a heterologous Helicobacter pylori coding sequence for whole H.pylori urease subunits A and B; disclosed whole H.pylori urease is a protective immunogen, discloses the open reading frames which encode H.pylori urease are known; and disclose the oral immunization of an animal with the recombinant Salmonella live vaccine vector (see col. 17, lines 12-67 and col. 18, lines 1-39; col. 19, lines 32-

67, and col. 20, lines 1-3) that encodes urease subunits A and B "fusion protein comprising the whole urease (see col. 19, line 54-56)".

Based upon the complete disclosure of Michetti et al, the instantly claimed invention is still anticipated.

15. The rejection of claims 24, 33-35 under 35 U.S.C. 102(b) as being anticipated by Michetti et al (WO95/22987), is traversed on the grounds that the reference "does not disclose the use of a recombinant cell which includes nucleic acids encoding both subunits and thus does not anticipate the present claims for the same reasons discussed above regarding Michetti (US Pat, 6,290,962).

16. It is the position of the examiner that Michetti et al discloses the recombinant expression of urease subunits A & B, utilizing a live attenuated vaccine Salmonella vector to induce a protective immune response:

(see page 17, paragraph 3; page 19, paragraph 2, lines 5-10; page 20, paragraph 3; "urease or its subunits see page 21, paragraph 3"; "recombinant Helicobacter pylori urease subunits page 22, paragraph 1"; genetically engineered attenuated live vectors of bacteria (see page 23, paragraph 2); mode of administration , page 25, paragraphs 2-3; page 27, paragraph 1 "whole urease (line 11)"; page 31, paragraph 3 "live vector" administration; and all claims).

For the same reasons set forth above for Michetti et al, US Pat. 6,290,962, the reference (WO95') still inherently anticipates the instantly claimed invention.

17. The rejection of Michetti et al (WO95') in view of Russell et al (US Pat. 6,030,624) is traversed on the grounds that Michetti et al does not disclose the use of a recombinant Salmonella cell which includes nucleic acid encoding both subunits, and the teachings of Russell et al do not cure the deficiencies discussed above.

18. It is the position of the examiner that Michetti et al does disclose, teach, suggest and provide guidance for the production, and immunization of an animal with a recombinant Salmonella live vaccine vector that comprises a heterologous nucleic acid that encodes the combination of both urease A& B subunit ("whole urease") coding sequences incorporated into a plasmid and Russell et al was cited to show the utilization of an AroA attenuated live vaccine vector for the expression of H.pylori antigens together with a cholera toxin subunit adjuvant.

(see Michetti, page 17, paragraph 3; page 19, paragraph 2, lines 5-10; page 20, paragraph 3; "urease or its subunits see page 21, paragraph 3"; "recombinant Helicobacter pylori urease subunits page 22, paragraph 1"; genetically engineered attenuated live vectors of bacteria (see page 23, paragraph 2); mode of administration , page 25, paragraphs 2-3; page 27, paragraph 1 "whole urease (line 11)"; page 31, paragraph 3 "live vector" administration; and all claims).

The combination of references sets forth a prima fascia case of obviousness, for reasons of record. No evidence of unexpected results has been provided to obviate this combination of references.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
April 28, 2004

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